

ATTACHMENT

*THE eCTD DOCUMENT INFORMATION BACKBONE FILES SPECIFICATION
FOR MODULES 2 THROUGH 5*

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1
2
3
4 **The ECTD Document Information Backbone Files**
5 **Specification for Modules 2 through 5**
6
7
8
9

10 This document provides specifications for creating the electronic common technical document
11 (eCTD) document information backbone file (eCTD backbone file). This specific document
12 discusses issues related to the creation of the eCTD backbone file for modules 2 to 5 for
13 electronic submission of applications for human pharmaceutical products and related
14 submissions to the FDA.

15 The module 2 to 5 eCTD backbone file includes document information for each document in
16 modules 2 to 5 and a hyperlink to the document. This information and hyperlink are provided
17 within an XML leaf element. The leaf elements in the module 1 eCTD backbone file are
18 organized using XML heading elements. The XML heading elements are named and organized
19 according to the subject matter of the documents.
20

21 The eCTD specifications are for a wide range of applications and related submission types. A
22 single submission will not use all the headings provided in modules 2 to 5. You should not
23 include XML heading elements that are not needed to organize the documents in your
24 submission to the Agency.
25

26 The remainder of this document provides details on the creation of the module 2 to 5 eCTD
27 backbone file.
28

29
30 **I. START AND FINISH OF THE MODULE 2 TO 5 ECTD BACKBONE FILE**
31

32 You should name the module 2 to 5 eCTD backbone file *index.xml* and place it in the main
33 submission folder as described in *Providing Regulatory Submissions in Electronic Format —*
34 *Human Pharmaceutical Applications and Related Submissions*.
35

36 The first elements and the last element¹ of the eCTD backbone file for modules 2 to 5 are
37 always the same. They contain machine-readable information about the following:
38

- 39
- 40 1. Version of XML being used
 - 41 2. Type of characters that are allowed in the file
 - 42 3. Location of the standards that control the organization of the XML Document
43 Information File

| ¹ [This is the end tag for the root element.](#)

44 4. Organization element and leaf element for the Module 1 ECTD backbone file
 45 5. Indication that the document information is ended (end tag)
 46
 47 A sample of the first elements common to all submissions followed by a comment and the last
 48 line of the XML Document Information File¹⁵ is provided below:
 49
 50 <?xml version = "1.0" encoding = "UTF-8"?>
 51 <!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-3-0.dtd">
 52 <ectd:ectd
 53 xmlns:ectd = "http://www.ich.org/ectd"
 54 xmlns:xlink = "http://www.w3c.org/1999/xlink">
 55 <m1-administrative-information-and-prescribing-information>
 56 <leaf
 57 ID="a1234567"
 58 operation="new"
 59 checksum="1234567"
 60 checksum-type="md5"
 61 xlink:href="m1/us/us-regional.xml">
 62 <title>Labeling and Administrative Document Information</title>
 63 </leaf>
 64 </m1-administrative-information-and-prescribing-information>
 65
 66 <!--This is a comment to indicate that the sample of XML elements shown
 67 above is the same for every "index.xml" file submitted to the FDA. All the
 68 heading elements and content for module 2, 3, 4, and module 5 will be
 69 provided after these elements and before the last element closing tag
 70 named </ectd:ectd> -->
 71
 72 </ectd:ectd>
 73

74 The elements used to organize document information for Modules 2 to 5 are placed within the
 75 area represented by the comment in the example shown above. Information about creating those
 76 elements is provided in other sections of this appendix.
 77
 78

79 II. INDIVIDUAL DOCUMENT INFORMATION; *LEAF ELEMENT*

81 Information for an individual document is contained in the *leaf* element, its attributes and its *title*
 82 element. The *leaf* element is used repeatedly throughout the eCTD backbone file to provide
 83 individual information for each document that is being submitted. This section will provide the
 84 following:
 85

- 86 1. Table with descriptions of the *leaf* element, attributes and title element used by the
 87 agency's automated document management systems (ADMS)
- 88 2. Sample *leaf* element code
- 89 3. Complete description of each part of the *leaf* element and different ways it can be used

91 **A. *leaf* element table**
92
93 The table below provides the name of each part of the *leaf* element² and a brief indication of its
94 purpose:
95

Part of "leaf" Element	Purpose of <i>leaf</i> Element Part
<leaf>	Tag indicating start of leaf element. Organizes document information for one document or for one XML Study Report Information File.
ID="a1234567"	ID attribute for leaf element. Provides a unique identification of this leaf element in the submission. Used by ADMS to locate document and its leaf information.
operation="new"	Operation attribute for leaf element. Provides information about this document's affect on the ADMS contents.
modified-file=""	Modified-file attribute for the leaf element. Provides the location of a previously submitted document and the action this document has on it. In this case it is empty because the document is new.
checksum="1234567"	Checksum attribute for leaf element. Provides the document's checksum value (Also known as document's "hash").
checksum-type="md5"	Checksum-type attribute for leaf element. Provides the type of checksum that is in the checksum attribute.
version="Version-1"	Version attribute for the leaf element. Provides information about the version of the document being provided.
xlink:href="m1/us/us-regional.xml"	Xlink:href attribute for the leaf element. Provides the location of the document (In this case, it is the relative path and filename).
xlink:show=""	A use for this attribute has not yet been defined within ICH and should have a null value, i.e., "".
<title>Labeling and Administrative Document Information</title>	Title element child of the leaf element. Provides the subject matter of the document for reviewer's understanding.
</leaf>	Tag indicating end of leaf element.

96
97
98 **B. *leaf* element example**
99
100 A sample of a single *leaf* element with the attributes and *title* element described in the previous
101 table is provided here:

102
103 <leaf
104 ID="a1234567"
105 operation="new"

² Each of the attributes is shown with arbitrary values within the quotation marks. The title element contains an arbitrary document title.

```
106     modified-file=""  
107     checksum="1234567"  
108     checksum-type="md5"  
109     xlink:href="m1/us/us-regional.xml"  
110     version="Version-1">  
111     <title>Labeling and Administrative Document Information</title>  
112   </leaf>  
113  
114   C. leaf element detail
```

116 For the remainder of this section each part of the leaf element is described in detail in its own
117 subsection.

118

119 1. Start Tag for the *leaf* Element

121 The purpose of the start tag is to provide machine-readable indications that document
122 information is beginning. All the *leaf* element attributes are contained within the start tag. The
123 title element is after the *leaf* element start tag.

124 The start tag for the *leaf* element begins with the "less than" sign, "<", and the lower case word
125 "leaf". This is followed by each of the *leaf* element attributes and their values. The *leaf* element,
126 its attributes and their values are placed between the word "leaf" and the last part of the *leaf*
127 element start tag. The last part of the start tag occurs after the last attribute value as the "greater
128 than" sign, ">".

129 The *leaf* element start tag and its matching end tag with all the attribute and element contents are
130 used for each document being submitted, modified or referenced³ to the Agency for review. The
131 *leaf* element is the fundamental block of information for every document and occurs throughout
132 all the XML Document Information Files. These include the eCTD backbone file for Module 1
133 and each of the eCTD Study Report Files.

134

135 2. *ID* Attribute for *leaf* Element

136 The purpose of the *leaf* element *ID* attribute is to provide a unique identification for the
137 document within the submission. The *leaf* element *ID* combined with the application number,
138 submission number and eCTD backbone file filename provide a unique ID for a document in
139 ADMS.

140 The *ID* attribute occurs after the word "leaf" and begins with the upper case letters "ID". The
141 value for the *ID* attribute is provided in a statement that begins with the equal sign and quotation
142 mark, ("="), followed by the *ID* attribute value and ending with a quotation mark. There should
143 be no spaces in the *ID* attribute value statement.

³Including previously submitted information. See *Guidance to Industry: Providing Regulatory Submissions in Electronic Format — Applications and Related Submissions* for more information.

148

149 The *ID* value should start with a letter followed by a combination of letters and numbers to
150 provide a unique identification of this leaf element within this XML Document Information File.
151 Examples of valid ID attributes:

152

153 ID="a1234567"
154 ID="id12235"
155 ID="pid1234"

156

157 The following are invalid values for the *ID* attribute:

158

159 ID="1234567" - does not start with a letter
160 ID="123E" - does not start with a letter
161 ID="a 1246" - space not allowed

162

163 You should provide an *ID* attribute and value for each *leaf* element.

164

165 3. *operation* attribute for the *leaf* element

166

167 The purpose of the *operation* attribute is to provide a machine-readable indication of the effect
168 this *leaf* has on ADMS. The action can be as simple as providing a new document or deleting an
169 old document. The action can also be more complex, for example to append, or replace an
170 existing document.

171

172 You should include an *operation* attribute for each document you are submitting. The value for
173 the operation attribute is limited to a selection from the following words: *new*, *append*, *replace*,
174 and *delete*. The table below provides each potential modified-file attribute and value with its
175 meaning:

176

Attribute and Value	Meaning in the ADMS
<i>operation=""</i>	<i>Operation</i> attribute with no value. The modified-file attribute will be ignored. This is the same as not including the attribute in the leaf element.
<i>operation = "new"</i>	<i>Operation</i> attribute value of new. This means that the document should be added to ADMS.
<i>operation = "append"</i>	<i>Operation</i> attribute value of append. This means there is an existing file in ADMS to which this new file should be added.
<i>operation = "replace"</i>	<i>Operation</i> attribute value of replace. This means there is an existing file in ADMS that this file replaces.
<i>operation = "delete"</i>	<i>Operation</i> attribute value of delete. This means there is an existing file in ADMS that should no longer be considered as part of the application. There may be no document provided for the leaf.

177

178

4. *modified-file* attribute for the *leaf* element

179
180 The purpose of the *modified-file* attribute is to provide the location of documents that are being
181 modified (i.e. replaced, amended or deleted) by the *leaf* element. The *modified-file* attribute
182 should have a value when the *operation* attribute has a value of *append*, *replace* or *delete*.
183
184 The *modified-file* attribute for the *leaf* element begins with the lowercase hyphenated word
185 "modified-file". The value for the *modified-file* attribute is provided in a statement that begins
186 with the equal sign and quotation mark, ("="), followed by the *modified-file* attribute value and
187 ending with a quotation mark. There should be no spaces in the *modified-file* attribute's value
188 statement.
189
190 The *modified-file leaf* attribute should have a value of a relative path and filename with a
191 bookmark. You should use the relative path and filename for the eCTD backbone file⁴
192 containing the modified document's leaf element. You should append the modified document's
193 leaf *ID* value to the relative path and file name as a bookmark. This is detailed in the next
194 paragraph.
195
196 The relative path and filename for a previously submitted document will start with two periods
197 and a slash, “..”, providing a machine readable instruction to move up one level in the directory
198 structure to where the previous submission folders are located. These characters are followed
199 with the sequence folder name (four numbers, e.g. 0001) and another slash. This is followed by
200 the path and filename for the modified document's eCTD backbone file⁵. This is followed by the
201 pound sign (#) and the *leaf ID* value for the document you want to modify.
202 An example of a modified file attribute value is provided below:
203
204 *modified-file*=“..0001/index.xml#a1234567”
205
206 This would provide the information needed to locate the file with the *leaf* element *ID* you
207 assigned as “a1234567” and provided in the sequence folder numbered “0001”.
208
209 If you provide a *modified-file* attribute with no value (i.e. no characters or spaces between the
210 quotation marks, *modified-file*=“””) it will be the same as not including the attribute in the leaf
211 element.
212
213 5. *checksum* attribute for the *leaf* element
214
215 The purpose of the *checksum* attribute is to provide the value of the checksum for the document
216 this leaf is providing. The checksum is the result of an algorithm that breaks down a document
217 into a unique series of characters. These characters are used to verify that the document was
218 transmitted and placed in ADMS without being modified⁶. Once the document is placed in

⁴ *index.xml*, *us-regional.xml* or *stf-study-report.xml* file. These are fully described in this section

⁵ That is, the *index.xml*, *us-regional.xml*, or *stf-study-report.xml* file used for the table of contents
of the submission in which the modified document was originally provided to the Agency.

⁶ Checksum value is also known as the document hash.

219 ADMS, the checksum algorithm is applied to the document again and the results are compared
220 with the value of the checksum attribute you provide.

221
222 The *checksum* attribute for the *leaf* element begins with the lowercase word "checksum". The
223 value for the *checksum* attribute is provided in a statement that begins with the equal sign and
224 quotation mark, ("="), followed by the *checksum* attribute value and ending with a quotation
225 mark. There should be no spaces in the *checksum* attribute's value statement. An example of a
226 *checksum* attribute and its value is provided:

227
228 *checksum*="e854d3002c02a61fe5cbe92fd97b0018"

229
230 You should provide a *checksum* attribute and value for every *leaf* element that provides a
231 document for the ADMS.

232
233 6. *checksum-type* attribute for the *leaf* element

234
235 The *checksum-type* attribute provides the name of the algorithm used to produce the checksum
236 value. It should unambiguously identify the algorithm being used.

237
238 The *checksum-type* attribute for the *leaf* element begins with the lowercase hyphenated word
239 "checksum-type". The value for the *checksum-type* attribute is provided in a statement that
240 begins with the equal sign and quotation mark, ("="), followed by the *checksum-type* attribute
241 value and ending with a quotation mark. There should be no spaces in the *checksum-type*
242 attribute's value statement. An example of a *checksum-type* attribute and its value is provided:

243
244 *checksum-type*="MD5"

245
246 You should provide a *checksum-type* attribute and value for every leaf element that contains a
247 checksum value.

248
249 7. *version* attribute for the *leaf* element

250
251 The purpose of the *version* attribute is to provide the applicant's internal version number for the
252 document being provided. For example, when the *leaf* element is providing access to a Study
253 Tagged File, the *version* attribute value should be the internal number or alphanumeric used to
254 identify the report.

255
256 The *version* attribute for the *leaf* element begins with the lowercase word "version". The value
257 for the *version* attribute is provided in a statement that begins with the equal sign and quotation
258 mark, ("="), followed by the *version* attribute value and ending with a quotation mark. There
259 should be no spaces in the *version* attribute's value statement. An example of a *version* attribute
260 and its value is provided:

261
262 *version*="Pneumonia-Study-1"

264 You should provide a *version* attribute and its value for every *leaf* element that provides a
265 document for ADMS.

266

267 8. *xlink:href* attribute for the *leaf* element

268

269 The purpose of the *xlink:href* attribute is to provide the machine-readable location and filename
270 of the document being provided to ADMS. The location is provided as the relative path and
271 filename of the document. The relative path should be provided relative to the eCTD backbone
272 file or Study Tagged File where the leaf is located.

273

274 The *xlink:href* attribute for the *leaf* element begins with the lowercase hyphenated word
275 "*xlink:href*". The value for the *xlink:href* attribute is provided in a statement that begins with the
276 equal sign and quotation mark, ("="), followed by the *xlink:href* attribute value and ending with a
277 quotation mark. There should be no spaces in the *xlink:href* attribute's value statement. An
278 example of a *xlink:href* attribute and its value is provided:

279

280 *xlink:href="m1/draft-label-1.pdf"*

281

282 You should provide an *xlink:href* attribute and its value for every *leaf* element that provides a
283 document for the ADMS.

284

285 9. *xlink:show* attribute

286

287 The ICH specification has not yet defined a use for the *xlink:show* attribute. You should have a
288 null value, (i.e., ""), for the *xlink:show* attribute.

289

290 10. *title* child element of the *leaf* element

291

292 The purpose of the *title* element is to provide a title for the file that is meaningful to the human
293 reader. The content of the *title* element is displayed to users that are browsing and searching
294 ADMS. You can use spaces, upper and lower case letters and numbers freely.

295

296 The *title* element begins with the "less than" sign, (<), and the lower case word "title", followed
297 by the "greater than" sign, (>). The *title* content is provided after the greater than sign. The *title*
298 element is ended similar to how it is started except a slash is placed between the less than sign
299 and the word "title". An example of a *title* element and its content is provided:

300

301 <title>Pneumonia Study in Pulmonary Challenged Infants</title>

302

303 You should provide a *title* element and content for every *leaf* element that provides a document
304 for ADMS.

305

306 11. End Tag for the *leaf* Element

307
308 The end tag for the *leaf* element is the same as the start tag except that it contains a "/" symbol
309 after the "less than" symbol, (</), used to start the tag. It occurs after the *title* element's end tag
310 and indicates the end of the document information for the *leaf* element.
311

312 III. ECTD MODULE ELEMENTS GENERAL DESCRIPTION

313
314 The *leaf* elements in the eCTD backbone file are organized according to the modules and
315 headings of the CTD. There is an XML element in the eCTD backbone file for each of the
316 headings and most of the subheadings of CTD. See *Subject Headings for eCTD Specifications*
317 for details. Each element has a start tag and an end tag. The element tags start with a "less than"
318 symbol, "<", and end with a "greater than" symbol, ">". The name of the element is inserted
319 between these symbols. The heading elements are completed with an end tag. The end tag is the
320 same as the start tag except it has a "slash", "/" after the "less than" symbol, (</). The content for
321 the element (i.e., subheading elements and *leaf* elements) occurs between the start tag and the
322 end tag. Multiple *leaf* elements can be provided within each subheading element. A sample
323 eCTD section with heading element, subheading element and leaf element is provided:
324
325

```
326 <m2-common-technical-document-summaries>
327   <m2-2-introduction>
328     <leaf
329       ID="a1234567"
330       operation="new"
331       checksum="1234567"
332       checksum-type="md5"
333       xlink:href="m2/CTD-introduction.pdf"
334       version="Version-1">
335       <title>Introduction to CTD Submission</title>
336     </leaf>
337   </m2-2-introduction>
338 </m2-common-technical-document-summaries>
```

339
340 This is an example of the way an isolated part of the Document Information File may appear.
341 Each of the heading elements for the eCTD Backbone file is described in detail in the section of
342 this appendix associated with the CTD module where the element occurs.
343

344 IV. ATTRIBUTES FOR ECTD MODULE ELEMENTS GENERAL DESCRIPTION

345
346 Some of the heading elements in the eCTD backbone file have attributes associated with them.
347 These elements are listed in the table under the heading "Heading element attributes reference
348 table" in this section. The attributes have different purposes that are each described in detail in
349 the section of this appendix associated with its Module. Each of heading element attributes
350 begins after the heading element name with a space followed by the lowercase attribute name.
351 The value for the attribute is provided in a statement that begins with the equal sign and

352 quotation mark, (""), followed by the attribute's value and ending with a quotation mark. There
353 should be no spaces in the attribute's value statement.

354
355 Some of the attributes occur for more than one element. For example, the "substance" attribute
356 occurs on both the Drug Substance element under Summaries and the Drug Substance element
357 under Body of Data as well as two of the appendices elements. You should make sure that the
358 attribute values each of these elements are coordinated so that they are the same when
359 appropriate. In the substance attribute example, the same value should be used for the Summary
360 and for the Body of Data Drug Substance heading elements. Likewise, the attribute named
361 "manufacturer" can have a different meaning in the Drug Substance heading element than it does
362 in the Drug Product heading element. The table, below, lists each heading element attribute
363 name and the element or elements where it can occur followed by the same information
364 organized with the heading elements listed and their associated attributes:
365

366 *1. Heading element attributes reference table*

Attribute Name	Applicable Heading Element(s)
substance	<m2-3-s-drug-substance> <m3-2-s-drug-substance> <m3-2-a-1-facilities-and-equipment> <m3-2-a-2-adventitious-agents-safety-evaluation>
manufacturer	<m2-3-s-drug-substance> <m2-3-p-drug-product> <m3-2-s-drug-substance> <m3-2-p-drug-product> <m3-2-a-1-facilities-and-equipment> <m3-2-a-2-adventitious-agents-safety-evaluation>
product-name	<m2-3-p-drug-product> <m3-2-p-drug-product> <m3-2-a-1-facilities-and-equipment> <m3-2-a-2-adventitious-agents-safety-evaluation>
dosageform	<m2-3-p-drug-product> <m3-2-p-drug-product> <m3-2-a-1-facilities-and-equipment> <m3-2-a-2-adventitious-agents-safety-evaluation>
excipient	<m3-2-p-4-control-of-excipients>
indication	<m2-7-3-summary-of-clinical-efficacy> <m5-3-5-reports-of-efficacy-and-safety-studies>
Heading Element	Applicable Attribute(s)
<m2-3-s-drug-substance>	substance manufacturer
<m2-3-p-drug-product>	product-name dosageform manufacturer
<m2-7-3-summary-of-clinical-efficacy>	indication

<m3-2-s-drug-substance>	substance manufacturer
<m3-2-p-drug-product>	product-name dosageform manufacturer
<m3-2-p-4-control-of-excipients>	excipient
<m3-2-a-1-facilities-and-equipment>	manufacturer substance dosageform product-name
<m3-2-a-2-adventitious-agents-safety-evaluation>	manufacturer substance dosageform product-name
<m5-3-5-reports-of-efficacy-and-safety-studies>	indication

368

369 Each of the heading element attributes for the eCTD backbone file is described in detail in the
 370 section of this appendix associated with the CTD module where the element and its attribute
 371 occur.

372

373 **V. MODULE 2: SUMMARIES**

374

375 This section includes a table of the heading and subheading elements with the corresponding
 376 CTD headings and subheadings and the attributes value descriptions for certain heading and
 377 subheading elements that used them to provide information to ADMS.

378

379

A. Module 2 Element Table

380

381 The table below provides CTD Module 2 heading and subheading organization with its
 382 corresponding eCTD element organization. In some cases, the CTD may describe more
 383 subheadings than appear on this table. Those subheadings should be used as bookmarks within
 384 the individual document. Both the start tag and end tag for each eCTD element are provided. If
 385 there are one or more subheadings for the CTD heading, the corresponding element end tag will
 386 occur on the table row below the last relevant subheading. Although there is a *leaf* element for
 387 each document under a subheading, *leaf* elements are not shown on this table to keep it clearer.
 388 The *leaf* elements should only occur as content for the eCTD heading element that is at the
 389 lowest possible level in the hierarchy. An eCTD heading element may contain any number of
 390 *leaf* elements. If no documents are submitted for a CTD heading, you should omit the element
 391 for that heading in the XML Document Information File.

392

Module 2 CTD Heading	eCTD Element
Module 2: Common Technical Document (CTD) Summaries	<m2-common-technical-document-summaries>
2.2 CTD Introduction	<m2-2-introduction> </m2-2-introduction>
Module 2: Quality Overall Summary	<m2-3-quality-overall-summary>

Module 2 CTD Heading	eCTD Element
(QOS)	
2.3 Introduction to the Quality Overall Summary	<m2-3-introduction> </m2-3-introduction>
2.3.S Drug Substance	<m2-3-s-drug-substance substance="" manufacturer=""> </m2-3-s-drug-substance> ⁷
2.3.P Drug Product	<m2-3-p-drug-product product-name="" dosageform="" manufacturer=""> </m2-3-p-drug-product> ⁸
2.3.A Appendices	<m2-3-a-appendices> </m2-3-a-appendices>
2.3.R Regional Information	<m2-3-r-regional-information> </m2-3-r-regional-information>
End QOS	</m2-3-quality-overall-summary>
Module 2: Nonclinical Overview	<m2-4-nonclinical-overview> </m2-4-nonclinical-overview>
Module 2: Nonclinical Written and Tabulated Summaries (NWTS)	<m2-6-nonclinical-written-and-tabulated-summaries>
2.6.1 Introduction	<m2-6-1-introduction> </m2-6-1-introduction>
2.6.2 Pharmacology Written Summary	<m2-6-2-pharmacology-written-summary> </m2-6-2-pharmacology-written-summary>
2.6.3 Pharmacology Tabulated Summary	<m2-6-3-pharmacology-tabulated-summary> </m2-6-3-pharmacology-tabulated-summary>
2.6.4 Pharmacokinetics Written Summary	<m2-6-4-pharmacokinetics-written-summary> </m2-6-4-pharmacokinetics-written-summary>
2.6.5 Pharmacokinetics Tabulated Summary	<m2-6-5-pharmacokinetics-tabulated-summary> </m2-6-5-pharmacokinetics-tabulated-summary>
2.6.6 Toxicology Written Summary	<m2-6-6-toxicology-written-summary> </m2-6-6-toxicology-written-summary>
2.6.7 Toxicology Tabulated Summary	<m2-6-7-toxicology-tabulated-summary> </m2-6-7-toxicology-tabulated-summary>
End NWTS	</m2-6-nonclinical-written-and-tabulated-summaries>
Module 2: Clinical Overview	<m2-5-clinical-overview> </m2-5-clinical-overview>
Module 2: Clinical Summary (CS)	<m2-7-clinical-summary>
2.7.1 Summary of Biopharmaceutic Studies and Associated	<m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods> </m2-7-1-summary-of-biopharmaceutic-studies-and-

⁷ See the description of element attributes after this table.

⁸ See the description of element attributes after this table.

Module 2 CTD Heading	eCTD Element
Analytical Methods	<associated-analytical-methods>
2.7.2 Summary of Clinical Pharmacology Studies	<m2-7-2-summary-of-clinical-pharmacology-studies> </m2-7-2-summary-of-clinical-pharmacology-studies>
2.7.3 Summary of Clinical Efficacy	<m2-7-3-summary-of-clinical-efficacy indication=""> </m2-7-3-summary-of-clinical-efficacy> ⁹
2.7.4 Summary of Clinical Safety	<m2-7-4-summary-of-clinical-safety> </m2-7-4-summary-of-clinical-safety>
2.7.5 References	<m2-7-5-literature-references> </m2-7-5-literature-references>
2.7.6 Synopses of Individual Studies	<m2-7-6-synopses-of-individual-studies> </m2-7-6-synopses-of-individual-studies>
End CS	</m2-7-clinical-summary>
End CTD Summaries	</m2-common-technical-document-summaries>

393

394

B. Attribute Values for Summary Heading Elements

395

396 Three of the eCTD Module 2 heading elements in the table, above, have attributes that contribute
 397 to ADMS operation. You should provide attribute values for each of these attributes. The
 398 attributes are discussed in detail each under its own heading:

399

400

1. Drug Substance Summary Element Attributes

401

402 The eCTD element for the Drug Substance Summary (DSS) heading, <m2-3-s-drug-substance>,
 403 has two attributes, *substance* and *manufacturer*. The purpose of these attributes is to provide
 404 human readable text to indicate the drug substance name or names and organizational headings
 405 for different manufacturers of the drug substance. These situations are more fully described in
 406 the *Guidance for Industry M4: The CTD-- Quality*. Instructions for creating an attribute and its
 407 value are provided in the section of this appendix that discusses attributes in general. An
 408 example of two DSS heading elements for different manufacturers of the same drug substance is
 409 provided:

410

```

411      <m2-common-technical-document-summaries>
412          <m2-3-quality-overall-summary>
413              <m2-3-s-drug-substance
414                  substance="Substace-USAN"
415                  manufacturer="Ohio">
416                  <leaf></leaf>10
417              </m2-3-s-drug-substance>
418              <m2-3-s-drug-substance
419                  substance="Substace-USAN"
420                  manufacturer="Louisiana">

```

⁹ See the description of element attributes after this table

¹⁰ Leaf element abbreviated for clarity.

2. Drug Product Summary Element Attributes

The eCTD element for the Drug Product Summary (DPS) heading, <m2-3-p-drug-product>, has three attributes, *product-name*, *dosageform* and *manufacturer*. The purpose of these attributes is to provide human readable text to indicate the drug product names and organizational headings for different dosage forms and the organizational headings for different manufacturers of the drug product. These situations are more fully described in the *Guidance for Industry M4: The CTD-- Quality*. Instructions for creating an attribute and its value are provided in the section of this appendix that discusses attributes in general. An example of two DPS heading elements for different manufacturers of the same dosage form and the same product name is provided:

```
444 <m2-common-technical-document-summaries>
445     <m2-3-quality-overall-summary>
446         <m2-3-p-drug-product
447             product-name="Cure All"
448             dosageform="Oral Tablet"
449             manufacturer="New-Jersey">
450             <leaf></leaf>13
451         </m2-3-p-drug-product>
452         <m2-3-p-drug-product
453             product-name="Cure All"
454             dosageform="Oral Tablet"
455             manufacturer="California">
456             <leaf></leaf>14
457         </m2-3-p-drug-product>
458     </m2-3-quality-overall-summary>
459 </m2-common-technical-document-summaries>
```

¹¹ Leaf element abbreviated for clarity.

¹² The leaf elements will be the same except for the leaf ID attribute value.

¹³ Leaf element abbreviated for clarity.

¹⁴ Leaf element abbreviated for clarity.

461 You should provide *product-name*, *dosageform* and *manufacturer* attribute values for every DPS
462 heading element. There is no limit to the number of DPS heading elements. If multiple DPS
463 heading elements are used, but much of the information for the two manufacturers or dosage
464 forms is shared information, place the shared information in documents separate from the
465 information that is not shared. The files with shared information will have leaf elements in both
466 DPS heading elements¹⁵. There is no limit to the number of leaf elements the DPS heading
467 element can contain.

468

469 3. *indication* Attribute for Summary of Clinical Efficacy Heading

470

471 The eCTD element for the Summary of Clinical Efficacy heading, <m2-7-3-summary-of-
472 clinical-efficacy>, has an attribute called *indication*. The purpose of the *indication* attribute is to
473 provide human readable abbreviation of the clinical indication being summarized under this
474 heading. If there is more than one indication for which a Summary of Clinical Efficacy (SCE) is
475 being submitted, you should create an additional SCE heading element for each indication. Each
476 SCE heading element should be the same except for the unique *indication* attribute value and
477 *leaf* content. Instructions for creating an attribute and its value are provided in the section of this
478 appendix that discusses attributes in general. An example of two *indication* attributes and their
479 values within two SCE heading elements is provided:

480

```
481       <m2-common-technical-document-summaries>
482            <m2-7-clinical-summary>
483              <m2-7-3-summary-of-clinical-efficacy indication="pneumonia">
484                <leaf></leaf>16
485              </m2-7-3-summary-of-clinical-efficacy>
486              <m2-7-3-summary-of-clinical-efficacy indication="sepsis">
487                <leaf></leaf>17
488              </m2-7-3-summary-of-clinical-efficacy>
489            </m2-7-clinical-summary>
490        </m2-common-technical-document-summaries>
```

491

492 You should provide an *indication* attribute value for every SCE heading element. There is no
493 limit to the number of SCE heading elements. If multiple SCE heading elements are used, but
494 much of the information for the two indications is shared information, place the shared
495 information in documents separate from the information that is not shared. The files with shared
496 information will have *leaf* elements in both SCE heading elements¹⁸. There is no limit to the
497 number of *leaf* elements the SCE heading element can contain.

498

499 **VI. MODULE 3: QUALITY**

500

¹⁵ The leaf elements will be the same except for the leaf ID attribute value.

¹⁶ Leaf element abbreviated for clarity.

¹⁷ Leaf element abbreviated for clarity.

¹⁸ The leaf elements will be the same except for the leaf ID attribute value.

501 This section includes a table of the heading and subheading elements with the corresponding
502 CTD headings and subheadings and the attributes value descriptions for certain heading and
503 subheading elements that used them to provide information to ADMS.

504

505 **A. Module 3 element table**

506

507 The table below provides CTD Module 3 heading and subheading organization with its
508 corresponding eCTD element organization. In some cases, the CTD may describe more
509 subheadings than appear on this table. Those subheadings should be used as bookmarks within
510 the individual document. Both the start tag and end tag for each eCTD element are provided. If
511 there are one or more subheadings for the CTD heading, the corresponding element end tag will
512 occur on the table row below the last relevant subheading. Although there is a *leaf* element for
513 each document under a subheading, *leaf* elements are not shown on this table to keep it clearer.
514 The *leaf* elements should only occur as content for the eCTD heading element that is at the
515 lowest possible level in the hierarchy. An eCTD heading element may contain any number of
516 *leaf* elements. If no documents are submitted for a CTD heading, you should omit the element
517 for that heading in the XML Document Information File.

518

519

Module 3 CTD Heading	eCTD Element
Module: 3 Quality	<m3-quality>
3.2 Body of Data	<m3-2-body-of-data>
3.2.S Drug Substance Name Manufacturer	<m3-2-s-drug-substance substance="" manufacturer=""> ¹⁹
3.2.S.1 General Information	<m3-2-s-1-general-information>
3.2.S.1.1 Nomenclature	<m3-2-s-1-1-nomenclature> </m3-2-s-1-1-nomenclature>
3.2.S.1.2 Structure	<m3-2-s-1-2-structure> </m3-2-s-1-2-structure>
3.2.S.1.3 General Properties	<m3-2-s-1-3-general-properties> </m3-2-s-1-3-general-properties>
End General Information	</m3-2-s-1-general-information>
3.2.S.2 Manufacture	<m3-2-s-2-manufacture>
3.2.S.2.1 Manufacturers	<m3-2-s-2-1-manufacturer> </m3-2-s-2-1-manufacturer>
3.2.S.2.2 Description of Manufacturing	<m3-2-s-2-2-description-of-manufacturing-process- and-process-controls> </m3-2-s-2-2-description-of-manufacturing-process- and-process-controls>
3.2.S.2.3 Control of Materials	<m3-2-s-2-3-control-of-materials> </m3-2-s-2-3-control-of-materials>

¹⁹ See the description of element attributes after this table.

Module 3 CTD Heading	eCTD Element
3.2.S.2.4 Controls of Critical Steps and Intermediates	<m3-2-s-2-4-controls-of-critical-steps-and-intermediates> </m3-2-s-2-4-controls-of-critical-steps-and-intermediates>
3.2.S.2.5 Process Validation and/or Evaluation	<m3-2-s-2-5-process-validation-and-or-evaluation> </m3-2-s-2-5-process-validation-and-or-evaluation>
3.2.S.2.6 Manufacturing Process Development	<m3-2-s-2-6-manufacturing-process-development> </m3-2-s-2-6-manufacturing-process-development>
End Manufacture	</m3-2-s-2-manufacture>
3.2.S.3 Characterization	<m3-2-s-3-characterisation>
3.2.S.3.1 Elucidation of Structure and other Characteristics	<m3-2-s-3-1-elucidation-of-structure-and-other-characteristics> </m3-2-s-3-1-elucidation-of-structure-and-other-characteristics>
3.2.S.3.2 Impurities	<m3-2-s-3-2-impurities> </m3-2-s-3-2-impurities>
End Characterization	</m3-2-s-3-characterisation>
3.2.S.4 Control of Drug Substance	<m3-2-s-4-control-of-drug-substance>
3.2.S.4.1 Specification	<m3-2-s-4-1-specification> </m3-2-s-4-1-specification>
3.2.S.4.2 Analytical Procedures	<m3-2-s-4-2-analytical-procedures> </m3-2-s-4-2-analytical-procedures>
3.2.S.4.3 Validation of Analytical Procedures	<m3-2-s-4-3-validation-of-analytical-procedures> </m3-2-s-4-3-validation-of-analytical-procedures>
3.2.S.4.4 Batch Analyses	<m3-2-s-4-4-batch-analyses> </m3-2-s-4-4-batch-analyses>
3.2.S.4.5 Justification of Specification	<m3-2-s-4-5-justification-of-specification> </m3-2-s-4-5-justification-of-specification>
End Control of Drug Substance	</m3-2-s-4-control-of-drug-substance>
3.2.S.5 Reference Standards or Materials	<m3-2-s-5-reference-standards-or-materials> </m3-2-s-5-reference-standards-or-materials>
3.2.S.6 Container Closure System	<m3-2-s-6-container-closure-system> </m3-2-s-6-container-closure-system>
3.2.S.7 Stability	<m3-2-s-7-stability>
3.2.S.7.1 Stability Summary and Conclusions	<m3-2-s-7-1-stability-summary-and-conclusions> </m3-2-s-7-1-stability-summary-and-conclusions>
3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment	<m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment> </m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment>
3.2.S.7.3 Stability Data	<m3-2-s-7-3-stability-data> </m3-2-s-7-3-stability-data>
End Stability	</m3-2-s-7-stability>

Module 3 CTD Heading	eCTD Element
End Drug Substance	</m3-2-s-drug-substance>
3.2.P Drug Product Name Dosage Form Manufacturer	<m3-2-p-drug-product product-name="" dosageform="" manufacturer=""> ²⁰
3.2.P.1 Description and Composition of the Drug Product	<m3-2-p-1-description-and-composition-of-the-drug-product> </m3-2-p-1-description-and-composition-of-the-drug-product>
3.2.P.2 Pharmaceutical Development	<m3-2-p-2-pharmaceutical-development> </m3-2-p-2-pharmaceutical-development>
3.2.P.3 Manufacture	<m3-2-p-3-manufacture>
3.2.P.3.1 Manufacturers	<m3-2-p-3-1-manufacturers> </m3-2-p-3-1-manufacturers>
3.2.P.3.2 Batch Formula	<m3-2-p-3-2-batch-formula> </m3-2-p-3-2-batch-formula>
3.2.P.3.3 Description of Manufacturing Process and Process Controls	<m3-2-p-3-3-description-of-manufacturing-process-and-process-controls> </m3-2-p-3-3-description-of-manufacturing-process-and-process-controls>
3.2.P.3.4 Controls of Critical Steps and Intermediates	<m3-2-p-3-4-controls-of-critical-steps-and-intermediates> </m3-2-p-3-4-controls-of-critical-steps-and-intermediates>
3.2.P.3.5 Process Validation and/or Evaluation	<m3-2-p-3-5-process-validation-and-or-evaluation> </m3-2-p-3-5-process-validation-and-or-evaluation>
End Manufacture	</m3-2-p-3-manufacture>
3.2.P.4 Control of Excipients	<m3-2-p-4-control-of-excipients excipient=""> ²¹
3.2.P.4.1 Specifications	<m3-2-p-4-1-specifications> </m3-2-p-4-1-specifications>
3.2.P.4.2 Analytical Procedures	<m3-2-p-4-2-analytical-procedures> </m3-2-p-4-2-analytical-procedures>
3.2.P.4.3 Validation of Analytical Procedures	<m3-2-p-4-3-validation-of-analytical-procedures> </m3-2-p-4-3-validation-of-analytical-procedures>
3.2.P.4.4 Justification of Specifications	<m3-2-p-4-4-justification-of-specifications> </m3-2-p-4-4-justification-of-specifications>
3.2.P.4.5 Excipients of Human or Animal Origin	<m3-2-p-4-5-excipients-of-human-or-animal-origin> </m3-2-p-4-5-excipients-of-human-or-animal-origin>
3.2.P.4.6 Novel Excipients	<m3-2-p-4-6-novel-excipients> </m3-2-p-4-6-novel-excipients>
End Control of Excipients	</m3-2-p-4-control-of-excipients>

²⁰ See the description of element attributes after this table.

²¹ See the description of element attributes after this table.

Module 3 CTD Heading	eCTD Element
3.2.P. 5 Control of Drug Product	<m3-2-p-5-control-of-drug-product>
3.2.P.5.1 Specifications	<m3-2-p-5-1-specifications> </m3-2-p-5-1-specifications>
3.2.P.5.2 Analytical Procedures	<m3-2-p-5-2-analytical-procedures> </m3-2-p-5-2-analytical-procedures>
3.2.P.5.3 Validation of Analytical Procedures	<m3-2-p-5-3-validation-of-analytical-procedures> </m3-2-p-5-3-validation-of-analytical-procedures>
3.2.P.5.4 Batch Analyses	<m3-2-p-5-4-batch-analyses> </m3-2-p-5-4-batch-analyses>
3.2.P.5.5 Characterization of Impurities	<m3-2-p-5-5-characterisation-of-impurities> </m3-2-p-5-5-characterisation-of-impurities>
3.2.P.5.6 Justification of Specifications	<m3-2-p-5-6-justification-of-specifications> </m3-2-p-5-6-justification-of-specifications>
End Control of Drug Product	</m3-2-p-5-control-of-drug-product>
3.2.P.6 Reference Standards or Materials	<m3-2-p-6-reference-standards-or-materials> </m3-2-p-6-reference-standards-or-materials>
3.2.P.7 Container Closure System	<m3-2-p-7-container-closure-system> </m3-2-p-7-container-closure-system>
3.2.P.8 Stability	<m3-2-p-8-stability>
3.2.P.8.1 Stability Summary and Conclusion	<m3-2-p-8-1-stability-summary-and-conclusion> </m3-2-p-8-1-stability-summary-and-conclusion>
3.2.P.8.2 Postapproval Stability Protocol and Stability Commitment	<m3-2-p-8-2-post-approval-stability-protocol-and-stability-commitment> </m3-2-p-8-2-post-approval-stability-protocol-and-stability-commitment>
3.2.P.8.3 Stability Data	<m3-2-p-8-3-stability-data> </m3-2-p-8-3-stability-data>
End Stability	</m3-2-p-8-stability>
End Drug Product	</m3-2-p-drug-product>
3.2.A APPENDICES	<m3-2-a-appendices>
3.2.A.1 Facilities and Equipment	<m3-2-a-1-facilities-and-equipment manufacturer="" substance="" dosageform="" product-name=""> ²² </m3-2-a-1-facilities-and-equipment
3.2.A.2 Adventitious Agents Safety Evaluation	<m3-2-a-2-adventitious-agents-safety-evaluation manufacturer="" substance="" dosageform="" product-name=""> ²³ </m3-2-a-2-adventitious-agents-safety-evaluation>

²² See the description of element attributes after this table.

²³ See the description of element attributes after this table.

Module 3 CTD Heading	eCTD Element
3.2.A.3 Novel Excipients	<m3-2-a-3-excipients> </m3-2-a-3-excipients>
End Appendices	</m3-2-a-appendices>
3.2.R REGIONAL INFORMATION	<m3-2-r-regional-information> </m3-2-r-regional-information>
End Body of Data	</m3-2-body-of-data>
3.3 LITERATURE REFERENCES	<m3-3-literature-references> </m3-3-literature-references>
End Quality	</m3-quality>

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523
524

Five of the eCTD Module 3 heading elements in the table, above, have attributes that contribute to the ADMS operation. You should provide attribute values for each of these attributes. The attributes and the used of their values is discussed in detail below each element under its own heading:

525 1. Drug Substance Element Attributes

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534

The eCTD element for the Drug Substance heading, <m3-2-s-drug-substance>, has two attributes, *substance* and *manufacturer*. The purpose of these attributes is to provide human readable text to indicate the drug substance name or names and organizational headings for different manufacturers of the drug substance. These situations are more fully described in the Guidance for Industry M4: The CTD-- Quality document. Instructions for creating an attribute and its value are provided in the section of this appendix that discusses attributes in general. An example of two Drug Substance heading elements for different manufacturers of the same drug substance is provided:

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```

<m3-quality>
  <m3-2-body-of-data>
    <m3-2-s-drug-substance
      substance="Cure All USP"
      manufacturer="China-DMF-999999">
      <leaf></leaf>24
    </m3-2-s-drug-substance>
    <m3-2-s-drug-substance
      substance=" Cure All USP "
      manufacturer="Louisiana">
      <leaf></leaf>25
    </m3-2-s-drug-substance>
  </m3-2-body-of-data >
</m3-quality >

```

551
552

You should provide *substance* and *manufacturer* attribute values for every Drug Substance heading element. There is no limit to the number of Drug Substance heading elements. If

²⁴ Leaf element abbreviated for clarity.

²⁵ Leaf element abbreviated for clarity.

553 multiple Drug Substance heading elements are used, but much of the information for the two
554 manufacturers is shared information, place the shared information in documents separate from
555 the information that is not shared. The files with shared information will have *leaf* elements in
556 both Drug Substance heading elements²⁶. There is no limit to the number of *leaf* elements the
557 Drug Substance heading element can contain.

558

559 2. Drug Product Summary Element Attributes

560

561 The eCTD element for the Drug Product heading, <m3-2-p-drug-product>, has three attributes,
562 *product-name*, *dosageform* and *manufacturer*. The purpose of these attributes is to provide
563 human readable text to indicate the drug product names and organizational headings for different
564 dosage forms and the organizational headings for different manufacturers of the drug product.
565 These situations are more fully described in the Guidance for Industry M4: The CTD-- Quality
566 document. An example of two Drug Product heading elements for different manufacturers of the
567 same dosage form and the same product name is provided:

568

```
569       <m3-quality>
570            <m3-2-body-of-data>
571              <m3-2-p-drug-product
572                product-name="Cure All"
573                dosageform="Injection"
574                manufacturer="China Plant 1 DMF-0000001">
575                <leaf></leaf>27
576            </ m3-2-p-drug-product >
577            <m3-2-p-drug-product
578              product-name="Cure All"
579              dosageform="Injection"
580              manufacturer="Puerto Rico Internal-Plant-#2">
581              <leaf></leaf>28
582            </m3-2-p-drug-product>
583          </ m3-2-body-of-data >
584        </m3-quality >
```

585

586 You should provide *product-name*, *dosageform* and *manufacturer* attribute values for every Drug
587 Product heading element. There is no limit to the number of Drug Product heading elements. If
588 multiple Drug Product heading elements are used, but much of the information for the two
589 manufacturers or dosage forms is shared information, place the shared information in documents
590 separate from the information that is not shared. The files with shared information will have *leaf*
591 elements in both Drug Product heading elements²⁹. There is no limit to the number of leaf
592 elements the Drug Product heading element can contain.

593

²⁶ The leaf elements will be the same except for the leaf ID attribute value.

²⁷ Leaf element abbreviated for clarity.

²⁸ Leaf element abbreviated for clarity.

²⁹ The leaf elements will be the same except for the leaf ID attribute value.

594 3. *excipient* Attribute for Control of Excipients Heading
595
596 The eCTD element for Control of Excipients, <m3-2-p-4-control-of-excipients>, has an attribute
597 called *excipient*. The purpose of the *excipient* attribute is to provide human readable text to
598 indicate the excipient for which information is being provided. If there is more than one
599 excipient, you should create an additional Control of Excipients heading element for each
600 excipient. An example of a Control of Excipients element with its *excipient* attribute is provided:
601

602 <m3-quality>
603 <m3-2-p-drug-product
604 product-name="Cure All"
605 dosageform="Injection"
606 manufacturer="China Plant 1 DMF-0000001">
607 <m3-2-p-4-control-of-excipients
608 excipient="corn syrup">
609 <m3-2-p-4-1-specifications>
610 <leaf></leaf>³⁰
611 </m3-2-p-4-1-specifications>
612 <m3-2-p-4-2-analytical-procedures>
613 <leaf></leaf>³¹
614 </m3-2-p-4-2-analytical-procedures>
615 <m3-2-p-4-4-justification-of-specifications>
616 <leaf></leaf>³²
617 </m3-2-p-4-4-justification-of-specifications>
618 </m3-2-p-4-control-of-excipients>
619 </m3-2-p-drug-product>
620 </m3-quality>
621

622 You should provide an *excipient* attribute value for every Control of Excipients heading element.
623 There is no limit to the number of Control of Excipients heading elements. If multiple Control of
624 Excipients heading elements are used, but much of the information is shared information, place
625 the shared information in documents separate from the information that is not shared. The files
626 with shared information will have *leaf* elements in both Control of Excipients heading
627 elements³³. There is no limit to the number of *leaf* elements the Control of Excipients heading
628 element can contain.
629

630 4. Attributes for Appendix Elements
631

632 The eCTD elements for the Facilities and Equipment heading, <m3-2-a-1-facilities-and-
633 equipment> and for the Adventitious Agents Safety Evaluation heading, <m3-2-a-2-
634 adventitious-agents-safety-evaluation>, each have four attributes, *manufacturer*, *substance*,

³⁰ Leaf element abbreviated for clarity.

³¹ Leaf element abbreviated for clarity.

³² Leaf element abbreviated for clarity.

³³ The leaf elements will be the same except for the leaf ID attribute value.

635 dosageform and product-name. The purpose of these attributes is to provide human readable text
636 to correlate the appendix with the manufacturer, drug substance, dosage form and drug product
637 name. These situations are more fully described in the Guidance for Industry M4: The CTD--
638 Quality document. An example of the Facilities and Equipment heading and the Adventitious
639 Agents Safety Evaluation heading elements with their attributes is provided:

640

```
641     <m3-quality>
642         <m3-2-a-appendices>
643             <m3-2-a-1-facilities-and-equipment
644                 manufacturer="China Plant 1 DMF-0000001"
645                 substance="Cures USP"
646                 dosageform="Injection"
647                 product-name="Cure All">
648                 <leaf></leaf>34
649             </m3-2-a-1-facilities-and-equipment
650             <m3-2-a-2-adventitious-agents-safety-evaluation
651                 manufacturer="Animal Extractions Inc"
652                 substance="Parts Substrate"
653                 dosageform="Injection"
654                 product-name="Cure All">
655                 <leaf></leaf>35
656             </m3-2-a-2-adventitious-agents-safety-evaluation>
657         </m3-2-a-appendices>
658     </m3-quality>
```

659

660 You should provide a *manufacturer*, *substance*, *dosageform* and *product-name* attribute and
661 value for every Facilities and Equipment heading and the Adventitious Agents Safety Evaluation
662 heading element. There is no limit to the number of Facilities and Equipment heading and the
663 Adventitious Agents Safety Evaluation heading elements. If multiple Facilities or Equipment
664 heading or Adventitious Agents Safety Evaluation heading elements are used, but much of the
665 information for the headings is shared information, place the shared information in documents
666 separate from the information that is not shared. The files with shared information will have *leaf*
667 elements in both heading elements³⁶. There is no limit to the number of *leaf* elements the
668 Facilities and Equipment and the Adventitious Agents Safety Evaluation heading elements can
669 contain.

670

671 VII. MODULE 4: SAFETY

672

673 This section includes a table of the heading and subheading elements with the corresponding
674 CTD headings and subheadings and the attributes value descriptions for certain heading and
675 subheading elements that used them to provide information to ADMS.

676

³⁴ Leaf element abbreviated for clarity.

³⁵ Leaf element abbreviated for clarity.

³⁶ The leaf elements will be the same except for the leaf ID attribute value.

677 The table below provides CTD Module 4 heading and subheading organization with its
 678 corresponding eCTD element organization. In some cases, the CTD may describe more
 679 subheadings than appear on this table. Those subheadings should be used as bookmarks within
 680 the individual document. Both the start tag and end tag for each eCTD element are provided. If
 681 there are one or more subheadings for the CTD heading, the corresponding element end tag will
 682 occur on the table row below the last relevant subheading. Although there is a *leaf* element for
 683 each document under a subheading, *leaf* elements are not shown on this table to keep it clearer.
 684 The *leaf* elements should only occur as content for the eCTD heading element that is at the
 685 lowest possible level in the hierarchy. An eCTD heading element may contain any number of
 686 *leaf* elements. If no documents are submitted for a CTD heading, you should omit the element
 687 for that heading in the XML Document Information File.
 688
 689

Module 4 CTD Heading	eCTD Element
Module 4: Nonclinical Study Reports	<m4-nonclinical-study-reports>
4.2 Study Reports	<m4-2-study-reports>
4.2.1 Pharmacology	<m4-2-1-pharmacology>
4.2.1.1 Primary Pharmacodynamics	<m4-2-1-1-primary-pharmacodynamics> </m4-2-1-1-primary-pharmacodynamics>
4.2.1.2 Secondary Pharmacodynamics	<m4-2-1-2-secondary-pharmacodynamics> </m4-2-1-2-secondary-pharmacodynamics>
4.2.1.3 Safety Pharmacology	<m4-2-1-3-safety-pharmacology> </m4-2-1-3-safety-pharmacology>
4.2.1.4 Pharmacodynamic Drug Interactions	<m4-2-1-4-pharmacodynamic-drug-interactions> </m4-2-1-4-pharmacodynamic-drug-interactions>
End Pharmacology	</m4-2-1-pharmacology>
4.2.2 Pharmacokinetics	<m4-2-2-pharmacokinetics>
4.2.2.1 Analytical Methods and Validation Reports	<m4-2-2-1-analytical-methods-and-validation-reports> </m4-2-2-1-analytical-methods-and-validation-reports>
4.2.2.2 Absorption	<m4-2-2-2-absorption> </m4-2-2-2-absorption>
4.2.2.3 Distribution	<m4-2-2-3-distribution> </m4-2-2-3-distribution>
4.2.2.4 Metabolism	<m4-2-2-4-metabolism> </m4-2-2-4-metabolism>
4.2.2.5 Excretion	<m4-2-2-5-excretion> </m4-2-2-5-excretion>
4.2.2.6 Pharmacokinetic Drug Interactions	<m4-2-2-6-pharmacokinetic-drug-interactions> </m4-2-2-6-pharmacokinetic-drug-interactions>
4.2.2.7 Other Pharmacokinetic Studies	<m4-2-2-7-other-pharmacokinetic-studies> </m4-2-2-7-other-pharmacokinetic-studies>
End Pharmacokinetics	</m4-2-2-pharmacokinetics>

Module 4 CTD Heading	eCTD Element
4.2.3 Toxicology	<m4-2-3-toxicology>
4.2.3.1 Single-Dose Toxicity	<m4-2-3-1-single-dose-toxicity> </m4-2-3-1-single-dose-toxicity>
4.2.3.2 Repeat-Dose Toxicity	<m4-2-3-2-repeat-dose-toxicity> </m4-2-3-2-repeat-dose-toxicity>
4.2.3.3 Genotoxicity	<m4-2-3-3-genotoxicity>
4.2.3.3.1 In vitro	<m4-2-3-3-1-in-vitro> </m4-2-3-3-1-in-vitro>
4.2.3.3.2 In vivo	<m4-2-3-3-2-in-vivo> </m4-2-3-3-2-in-vivo>
End Genotoxicity	</m4-2-3-3-genotoxicity>
4.2.3.4 Carcinogenicity	<m4-2-3-4-carcinogenicity>
4.2.3.4.1 Long-term studies	<m4-2-3-4-1-long-term-studies> </m4-2-3-4-1-long-term-studies>
4.2.3.4.2 Short- or medium-term studies	<m4-2-3-4-2-short-or-medium-term-studies> </m4-2-3-4-2-short-or-medium-term-studies>
4.2.3.4.3 Other studies	<m4-2-3-4-3-other-studies> </m4-2-3-4-3-other-studies>
End Carcinogenicity	</m4-2-3-4-carcinogenicity>
4.2.3.5 Reproductive and Developmental Toxicity	<m4-2-3-5-reproductive-and-developmental-toxicity>
4.2.3.5.1 Fertility and early embryonic development	<m4-2-3-5-1-fertility-and-early-embryonic-development> </m4-2-3-5-1-fertility-and-early-embryonic-development>
4.2.3.5.2 Embryofetal development	<m4-2-3-5-2-embryo-fetal-development> </m4-2-3-5-2-embryo-fetal-development>
4.2.3.5.3 Prenatal and postnatal development, including maternal function	<m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function> </m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function>
4.2.3.5.4 Studies in which the offspring	<m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated> </m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated>
End Reproductive Toxicology	</m4-2-3-5-reproductive-and-developmental-toxicity>
4.2.3.6. Local Tolerance	<m4-2-3-6-local-tolerance> </m4-2-3-6-local-tolerance>
4.2.3.7. Other Toxicity Studies	<m4-2-3-7-other-toxicity-studies>
4.2.3.7.1 Antigenicity	<m4-2-3-7-1-antigenicity> </m4-2-3-7-1-antigenicity>

Module 4 CTD Heading	eCTD Element
4.2.3.7.2 Immunotoxicity	<m4-2-3-7-2-immunotoxicity> </m4-2-3-7-2-immunotoxicity>
4.2.3.7.3 Mechanistic studies	<m4-2-3-7-3-mechanistic-studies> </m4-2-3-7-3-mechanistic-studies>
4.2.3.7.4 Dependence	<m4-2-3-7-4-dependence> </m4-2-3-7-4-dependence>
4.2.3.7.5 Metabolites	<m4-2-3-7-5-metabolites> </m4-2-3-7-5-metabolites>
4.2.3.7.6 Impurities	<m4-2-3-7-6-impurities> </m4-2-3-7-6-impurities>
4.2.3.7.7 Other	<m4-2-3-7-7-other> </m4-2-3-7-7-other>
End Other	</m4-2-3-7-other-toxicity-studies>
End Toxicology	</m4-2-3-toxicology>
End Study Reports	</m4-2-study-reports>
4.3 Literature References	<m4-3-literature-references> </m4-3-literature-references>
End Nonclinical	</m4-nonclinical-study-reports>

690

691 An example of the elements used to organize the *leaf* element for the Embryo Fetal Development
 692 Toxicology heading document is provided:

693

```

694      <m4-nonclinical-study-reports>
695          <m4-2-study-reports>
696              <m4-2-3-toxicology>
697                  <m4-2-3-5-reproductive-and-developmental-toxicity>
698                      <m4-2-3-5-2-embryo-fetal-development>
699                          <leaf></leaf>37
700                  </m4-2-3-5-2-embryo-fetal-development>
701          </m4-2-3-reproductive-and-developmental-toxicity>
702      </m4-2-3-toxicology>
703      </m4-2-study-reports>
704  </m4-nonclinical-study-reports>
705
  
```

706 If multiple heading elements are used and information for the headings is shared information,
 707 place the shared information in documents separate from the information that is not shared. The
 708 files with shared information will have *leaf* elements in both heading elements³⁸. The number of
 709 *leaf* elements that the heading elements can contain is not limited.

710

711 **VIII. MODULE 5: EFFICACY**

712

³⁷ Leaf element abbreviated for clarity.

³⁸ The leaf elements will be the same except for the leaf ID attribute value.

713 This section includes a table of the heading and subheading elements with the corresponding
714 CTD headings and subheadings and the attributes value descriptions for certain heading and
715 subheading elements that used them to provide information to ADMS.

716

717 **A. Module 5 element table**

718

719 The table below provides CTD Module 5 heading and subheading organization with its
720 corresponding eCTD element organization. In some cases, the CTD may describe more
721 subheadings than appear on this table. Those subheadings should be used as bookmarks within
722 the individual document. Both the start tag and end tag for each eCTD element are provided. If
723 there are one or more subheadings for the CTD heading, the corresponding element end tag will
724 occur on the table row below the last relevant subheading. Although there is a *leaf* element for
725 each document under a subheading, *leaf* elements are not shown on this table to keep it clearer.
726 The *leaf* elements should only occur as content for the eCTD heading element that is at the
727 lowest possible level in the hierarchy. An eCTD heading element may contain any number of
728 *leaf* elements. If no documents are submitted for a CTD heading, you should omit the element
729 for that heading in the XML Document Information File.

730

731

Module 5 CTD Heading	eCTD Element
Module 5: Clinical Study Reports	<m5-clinical-study-reports>
5.2 Tabular Listing Of All Clinical Studies	<m5-2-tabular-listing-of-all-clinical-studies> </m5-2-tabular-listing-of-all-clinical-studies>
5.3 Clinical Study Reports And Related Information	<m5-3-clinical-study-reports>
5.3.1 Reports Of Biopharmaceutic Studies	<m5-3-1-reports-of-biopharmaceutic-studies >
5.3.1.1 Bioavailability (BA) Study Reports	<m5-3-1-1-bioavailability-study-reports> </m5-3-1-1-bioavailability-study-reports>
5.3.1.2 Comparative BA And Bioequivalence (BE) Study Reports	<m5-3-1-2-comparative-ba-and-bioequivalence-study-reports> </m5-3-1-2-comparative-ba-and-bioequivalence-study-reports>
5.3.1.3 In Vitro-In Vivo Correlation Study Reports	<m5-3-1-3-in-vitro-in-vivo-correlation-study-reports> </m5-3-1-3-in-vitro-in-vivo-correlation-study-reports>
5.3.1.4 Reports Of Bioanalytical And Analytical Methods For Human Studies	<m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies> </m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies>
End Biopharm	</m5-3-1-reports-of-biopharmaceutic-studies>
5.3.2 Reports Of Studies Pertinent To Pharmacokinetics Using Human Biomaterials	<m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials>

Module 5 CTD Heading	eCTD Element
5.3.2.1 Plasma Protein Binding Study Reports	<m5-3-2-1-plasma-protein-binding-study-reports> </m5-3-2-1-plasma-protein-binding-study-reports>
5.3.2.2 Reports Of Hepatic Metabolism And Drug Interaction Studies	<m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies> </m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies>
5.3.2.3 Reports Of Studies Using Other Human Biomaterials	<m5-3-2-3-reports-of-studies-using-other-human-biomaterials> </m5-3-2-3-reports-of-studies-using-other-human-biomaterials>
End Human Biomaterials	</m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials>
5.3.3 Reports Of Human Pharmacokinetic (PK) Studies	<m5-3-3-reports-of-human-pharmacokinetics-pk-studies>
5.3.3.1 Healthy Subject PK And Initial Tolerability Study Reports	<m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports> </m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports>
5.3.3.2 Patient PK And Initial Tolerability Study Reports	<m5-3-3-2-patient-pk-and-initial-tolerability-study-reports> </m5-3-3-2-patient-pk-and-initial-tolerability-study-reports>
5.3.3.3 Intrinsic Factor Pk Study Reports	<m5-3-3-3-intrinsic-factor-pk-study-reports> </m5-3-3-3-intrinsic-factor-pk-study-reports>
5.3.3.4 Extrinsic Factor Pk Study Reports	<m5-3-3-4-extrinsic-factor-pk-study-reports> </m5-3-3-4-extrinsic-factor-pk-study-reports>
5.3.3.5 Population Pk Study Reports	<m5-3-3-5-population-pk-study-reports> </m5-3-3-5-population-pk-study-reports>
End PK	</m5-3-3-reports-of-human-pharmacokinetics-pk-studies>
5.3.4 Reports Of Human Pharmacodynamic (PD) Studies	<m5-3-4-reports-of-human-pharmacodynamics-pd-studies>
5.3.4.1 Healthy Subject PD And PK/PD Study Reports	<m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports> </m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports>
5.3.4.2 Patient PD And PK/PD Study Reports	<m5-3-4-2-patient-pd-and-pk-pd-study-reports> </m5-3-4-2-patient-pd-and-pk-pd-study-reports>

Module 5 CTD Heading	eCTD Element
	</m5-3-4-reports-of-human-pharmacodynamics-pd-studies>
5.3.5 Reports Of Efficacy And Safety Studies	<m5-3-5-reports-of-efficacy-and-safety-studies indication=""> ³⁹
5.3.5.1 Study Reports Of Controlled Clinical Studies Pertinent To The Claimed Indication	<m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication> </m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
5.3.5.2 Study Reports Of Uncontrolled Clinical Studies	<m5-3-5-2-study-reports-of-uncontrolled-clinical-studies> </m5-3-5-2-study-reports-of-uncontrolled-clinical-studies>
5.3.5.3 Reports Of Analyses Of Data From More Than One Study	<m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study> </m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study>
5.3.5.4 Other Study Reports	<m5-3-5-4-other-study-reports> </m5-3-5-4-other-study-reports>
End Efficacy and Safety	</m5-3-5-reports-of-efficacy-and-safety-studies>
5.3.6 Reports Of Postmarketing Experience	<m5-3-6-reports-of-postmarketing-experience> </m5-3-6-reports-of-postmarketing-experience>
5.3.7 Case Report Forms And Individual Patient Listings	<m5-3-7-case-report-forms-and-individual-patient-listings> </m5-3-7-case-report-forms-and-individual-patient-listings>
5.4 literature References	<m5-4-literature-references> </m5-4-literature-references>
End Module 5	<m5-clinical-study-reports>

732

733 **B. *indication* Attribute for Summary of Clinical Efficacy Heading**

734

735 The eCTD element for the Reports of Efficacy And Safety Studies (ES) heading, <m5-3-5-
 736 reports-of-efficacy-and-safety-studies >, has an attribute called *indication*. The purpose of the
 737 *indication* attribute is to provide human readable abbreviation of the clinical indication being
 738 summarized under this heading. If there is more than one indication being claimed, you should
 739 create an additional ES heading element for each indication. Each ES heading element should be
 740 the same except for the unique *indication* attribute value and *leaf* content.

741

742 The indication attribute for the ES heading element begins after the element name with a space
 743 and the lowercase word *indication*. The value for the *indication* attribute is provided in a
 744 statement that begins with the equal sign and quotation mark, (="), followed by the indication
 745 attribute value and ending with a quotation mark. There should be no spaces in the indication

³⁹ See the description of element attributes after this table.

746 attribute's value statement. An example of two indication attributes and their values within two
747 ES heading elements is provided:

748

```
749     <m5-clinical-study-reports>
750         <m5-3-clinical-study-reports>
751             <m5-3-5-reports-of-efficacy-and-safety-studies
752                 indication="pneumonia ">
753                 <leaf></leaf>40
754             </m5-3-5-reports-of-efficacy-and-safety-studies >
755             <m5-3-5-reports-of-efficacy-and-safety-studies
756                 indication="sepsis">
757                 <leaf></leaf>41
758             </m5-3-5-reports-of-efficacy-and-safety-studies>
759         </m5-3-clinical-study-reports>
760     </m5-clinical-study-reports>
```

761

762 You should provide an *indication* attribute value for every ES heading element. There is no limit
763 to the number of ES heading elements. If multiple ES heading elements are used, but much of
764 the information for the two indications is shared information, place the shared information in
765 documents separate from the information that is not shared. The files with shared information
766 will have *leaf* elements in both ES heading elements⁴². There is no limit to the number of *leaf*
767 elements the ES heading element can contain.

768

769 IX. ECTD EXAMPLE TEMPLATE

770

771 This is an example of a complete eCTD backbone with every heading and subheading. Blank
772 *leaf* elements are provided at each position where they should appear. If your electronic
773 submission does not use a specific heading element to contain a *leaf* element, you should leave it
774 off the eCTD submission. For example, you should not provide empty heading elements. The
775 *leaf* elements should be provided only as content for the eCTD-heading element that is at the
776 lowest possible level in the hierarchy. An eCTD-heading element may contain any number of
777 *leaf* elements.

778

```
779
780 <?xmlversion = "1.0" encoding = "UTF-8"?>
781 <!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-3-0.dtd">
782 <ectd:ectd
783     xmlns:ectd = "http://www.ich.org/ectd"
784     xmlns:xlink = "http://www.w3c.org/1999/xlink">
785
786 <!-- M1 Regional Module Link -->
```

⁴⁰ Leaf element abbreviated for clarity.

⁴¹ Leaf element abbreviated for clarity.

⁴² The leaf elements will be the same except for the leaf element's ID attribute, checksum attribute, and checksum-type attribute values.

```

787
788 <m1-administrative-information-and-prescribing-information>
789   <leaf
790     ID="id127"
791     operation="new"
792     checksum=""
793     checksum-type=""
794     xlink:href="m1/us/us-regional.xml">
795     <title>Labeling and Administrative Document Information</title>
796   </leaf>
797 </m1-administrative-information-and-prescribing-information>
798
799 <!-- M2 Summary Module -->
800
801 <m2-common-technical-document-summaries>
802   <m2-2-introduction>
803     <leaf ID="id002" operation="new" checksum="" checksum-type="" xlink:href="">
804       <title></title></leaf>
805   </m2-2-introduction>
806   <m2-3-quality-overall-summary>
807     <m2-3-introduction>
808       <leaf ID="id003" operation="new" checksum="" checksum-type="" xlink:href="">
809         <title></title></leaf>
810     </m2-3-introduction>
811     <m2-3-s-drug-substance
812       substance=""
813       manufacturer="">
814       <leaf ID="id004" operation="new" checksum="" checksum-type="" xlink:href="">
815         <title></title></leaf>
816     </m2-3-s-drug-substance>
817     <m2-3-p-drug-product
818       product-name=""
819       dosageform=""
820       manufacturer="">
821       <leaf ID="id005" operation="new" checksum="" checksum-type="" xlink:href="">
822         <title></title></leaf>
823     </m2-3-p-drug-product>
824     <m2-3-a-appendices>
825       <leaf ID="id006" operation="new" checksum="" checksum-type="" xlink:href="">
826         <title></title></leaf>
827     </m2-3-a-appendices>
828     <m2-3-r-regional-information>
829       <leaf ID="id007" operation="new" checksum="" checksum-type="" xlink:href="">
830         <title></title></leaf>
831     </m2-3-r-regional-information>
832   </m2-3-quality-overall-summary>

```

```
833 <m2-4-nonclinical-overview>
834 <leaf ID="id008" operation="new" checksum="" checksum-type="" xlink:href="">
835 <title></title></leaf>
836 </m2-4-nonclinical-overview>
837 <m2-5-clinical-overview>
838 <leaf ID="id016" operation="new" checksum="" checksum-type="" xlink:href="">
839 <title></title></leaf>
840 </m2-5-clinical-overview>
841 <m2-6-nonclinical-written-and-tabulated-summaries>
842 <m2-6-1-introduction>
843 <leaf ID="id009" operation="new" checksum="" checksum-type="" xlink:href="">
844 <title></title></leaf>
845 </m2-6-1-introduction>
846 <m2-6-2-pharmacology-written-summary>
847 <leaf ID="id010" operation="new" checksum="" checksum-type="" xlink:href="">
848 <title></title></leaf>
849 </m2-6-2-pharmacology-written-summary>
850 <m2-6-3-pharmacology-tabulated-summary>
851 <leaf ID="id011" operation="new" checksum="" checksum-type="" xlink:href="">
852 <title></title></leaf>
853 </m2-6-3-pharmacology-tabulated-summary>
854 <m2-6-4-pharmacokinetics-written-summary>
855 <leaf ID="id012" operation="new" checksum="" checksum-type="" xlink:href="">
856 <title></title></leaf>
857 </m2-6-4-pharmacokinetics-written-summary>
858 <m2-6-5-pharmacokinetics-tabulated-summary>
859 <leaf ID="id013" operation="new" checksum="" checksum-type="" xlink:href="">
860 <title></title></leaf>
861 </m2-6-5-pharmacokinetics-tabulated-summary>
862 <m2-6-6-toxicology-written-summary>
863 <leaf ID="id014" operation="new" checksum="" checksum-type="" xlink:href="">
864 <title></title></leaf>
865 </m2-6-6-toxicology-written-summary>
866 <m2-6-7-toxicology-tabulated-summary>
867 <leaf ID="id015" operation="new" checksum="" checksum-type="" xlink:href="">
868 <title></title></leaf>
869 </m2-6-7-toxicology-tabulated-summary>
870 </m2-6-nonclinical-written-and-tabulated-summaries>
871 <m2-7-clinical-summary>
872 <m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods>
873 <leaf ID="id017" operation="new" checksum="" checksum-type="" xlink:href="">
874 <title></title></leaf>
875 </m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods>
876 <m2-7-2-summary-of-clinical-pharmacology-studies>
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